correcting said calculated concentrations of constituent components as a function of wavelength.--

--36. The method of claim 26, said correcting step comprising,

correcting said calculated concentrations of constituent components as a function of wavelength.--

REMARKS

This paper amends claims 1, 12, and 30, and adds new claims 34-36. Claims 1-36 remain in this application. The fee for the additional three dependent claims is enclosed.

FORMAL MATTERS

a. Drawings

The indication of drawing informality is noted. Formal drawings will be prepared and filed upon an indication of allowable subject matter.

The Notice of Draftsman's Patent Drawing Review indicates that the copyright notice appearing on Figures 11A - 11D should be removed. Applicants respectfully decline to do this.

As explained in the specification, Figures 11A-D present a computer program that is written in a graphical language (see, specification, page 11, lines 29-30, and page 20, lines 7-12). A copyright notice has been properly included on the computer program listing, and the appropriate authorization has been included at the beginning of the specification (page 2, lines 1-6). *See,* MPEP § 608.01(v); *also see, In re Yardley*, 181 U.S.P.Q. 331 (C.C.P.A. 1974)

(copyright and patent protection for design may exist contemporaneously). Withdrawal of the requirement to remove the copyright notice from Figures 11A-D is respectfully requested.

b. Declaration and Abstract

Appended to the subject Office Action was a Notice of Informal Application noting discrepancies in the Declaration and indicating that the original abstract was too long.

Filed herewith is a new abstract typed on a separate sheet. The new abstract is an edited version of the original abstract, and no new matter has been added. Withdrawal of the objection to the abstract is respectfully requested.

In response to the requirement for a new Declaration, filed herewith is a Substitute Declaration signed by each of the inventors and listing their residence addresses. It should be noted, as explained on the Substitute Declaration, that the post office addresses are the same as the residence addresses of each of the inventors, and these lines are therefore blank. Withdrawal of the objection to the Declaration is respectfully requested.

In addition, the enclosed Substitute Declaration claims priority under 35 U.S.C. § 120 of prior application Serial No. 07/313,911, filed February 23, 1989, now abandoned. As expressly permitted by § 120, the specification has been amended accordingly to indicate that the present application is a continuation-in-part of this parent application.

When the prior application became abandoned, all pending claims were under final rejection under 35 U.S.C. § 103 as being unpatentable over the teachings of Anderson, *et al.*, "Light-Absorbing and Scattering Properties of Non-Haemolysed Blood," *Phys. Med. Bio.*, Vol. 12, 2:173-184 (1967), taken with Brown, *et al.*, U.S. Patent No. 4,134,678, with or without

Shibata, *et al.*, U.S. Patent No. 3,516,746. Appeal of the rejection was affirmed by the Board of Appeals. Each of these references is of record in the present application. Parent application serial number 07/313,911 was pending in Art Unit 255, under examination by Richard A. Rosenberger.

The present application includes substantial supplementation and expansion of the disclosure of the prior application. In addition, the claims presently pending in this application are directed to this expanded disclosure. This claim for priority under § 120 does not eliminate any pending prior art rejections, but is simply to bring to the attention of the Patent Office the existence of this prior application.

REJECTION OF CLAIMS UNDER §§ 102 AND 103

Claims 1, 10, 20-24 and 26-27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Anderson, et al. In addition, claims 2-9, 11-19, 25 and 28-33 stand rejected under 35 U.S.C. § 103 as being unpatentable over Anderson, et al. Applicants respectfully traverse this rejection.

Examiner Hantis and Primary Examiner McGraw are thanked for the courtesies extended during the interview of January 19, 1994. The points brought forth during that interview are rearticulated and expanded upon in this paper.

As promised during the interview, filed herewith are the Declarations under 37 C.F.R. § 1.132 of two experts in the optical properties of blood -- Dr. Joseph M. Schmitt and Dr.

Roland N. Pittman.[1] As explained in more detail below, each of these experts has reviewed the pending application and claims, along with the applied Anderson *et al.* reference, and each conclude that the reference has been misconstrued, and that the rejected claims should not be considered obvious in light of the Anderson *et al.* reference.

Specifically, the present invention is a method of determining the concentrations of a plurality of constituent components of unaltered whole blood of unknown composition. As stated in sole independent claim 1, the method requires the generation of a plurality of radiation wavelengths -- an absorbance subset of wavelengths and a scattering subset of wavelengths. The absorbance subset of wavelengths is selected to minimize the effects of radiation scattering and to maximize radiation absorbance by the constituent components, and the scattering subset of wavelengths is selected to maximize the effects of radiation scattering by unaltered whole blood relative to the effects of radiation absorbance.

The sample of unaltered whole blood is irradiated with the plurality of radiation wavelengths through a depth of the sample chosen to minimize radiation scattering, and the intensities of the radiation wavelengths are detected after passing through the depth of the sample at a distance from the sample and over detecting area, both chosen to minimize the effects of radiation scattering. Finally, the method requires the calculation of the concentrations of the plurality of constituent components, corrected for the effects of radiation scattering, as a function of the detected intensities, and as a function of predetermined molar extinction coefficients for each of the constituent components at each of the plurality of wavelengths.

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[1] Citation to the Declaration of Dr. Schmitt will be "Schmitt, ¶____", and citation to the Declaration of Dr. Pittman will be "Pittman, ¶_____".

Therefore, the present invention has as its fundamental purpose the determination of the concentration of the constituent components of unaltered whole blood of unknown composition. In contrast, the purposes of Anderson *et al.* (Anderson *et al.*, p. 174, second full paragraph) were:

> "(a) to investigate the light-scattering and light-absorbing properties of non-haemolyzed blood,
>
> (b) to evaluate separately the amount of light absorbed and the amount scattered by thin layers of flowing non-haemolyzed blood by applying a theory for the multiple scattering of waves, and
>
> (c) to test the general validity of the empirical relationships between OD[optical density] and haemoglobin content (eqn. (1))."

Not stated among the purposes of Anderson *et al.* was the determination of hemoglobin concentration, or the determination of the concentration of any other blood constituent component, from optical density. Pittman, ¶ 5; Schmitt, ¶ 5.

In contrast, sole independent claim 1 requires "determining the concentration of a plurality of constituent components of unaltered whole blood of unknown composition." Anderson *et al.* thus do not even seek to accomplish what the presently claimed invention does.

The theory being tested by Anderson *et al.* is Twersky's theory which describes the multiple scattering of waves by randomly distributed particles (Anderson *et al.*, page 174, third full paragraph; Pittman, ¶ 5; Schmitt, ¶ 5). To test Twersky's theory, Anderson *et al.* used altered whole blood in form of "non-haemolysed red cells suspended in isotonic saline." Anderson *et al.*, page 177, second paragraph; Pittman, ¶ 11; Schmitt, ¶ 11.

Therefore, what Anderson *et al.* did was create suspensions of red blood cells in isotonic saline, and determine the hemoglobin concentration of the altered samples by some unspecified means. Then, Anderson *et al.* measured the optical density of the suspended red cells, and plotted this optical density against the measured hemoglobin concentration. They then used curved-fitting techniques by employing arbitrary values for various parameters in Twersky's equation (Anderson *et al.*, eq. 5, page 175). The parameters in Twersky's equation that were set to arbitrary constant values to accomplish curve fitting include the parameter s and q_α/q (Anderson *et al.*, page 180, last paragraph; Pittman, ¶ 6; Schmitt, ¶ 6).

Applicants respectfully assert that, contrary to the Examiner's contention, Anderson *et al.* did not develop a practical method for deducing the concentration of the constituent components of whole blood from optical density.

This is because it is in fact impossible to solve Twersky's equation (the fundamental theory underlying the Anderson *et al.* paper), for a sample of whole blood of unknown composition. The reason for this mathematical impossibility is that Twersky's equation contains too many parameters for which there is no known value in a sample of whole blood of unknown composition. Pittman, ¶ 8; Schmitt, ¶ 8.

Specifically, equation 5 of Anderson *et al.* (page 175), requires the use of specific values for the parameters K′, s and q_α/q, which together quantify the refractive index of the liquid suspending the red cells (in this case, isotonic saline), the refractive index of red cells, and a factor L which depends on the size and shape of the red blood cells. Since each of these factors may vary in an unpredictable way from one blood sample to another, it is therefore not possible

to solve Twersky's equation for hemoglobin concentration in a sample of whole blood of unknown composition. Pittman, ¶ 9; Schmitt, ¶ 9.

Moreover, the four parameters in Twersky's equation that quantify scattering (K′, s and q_α/q), do not accommodate causes of scattering other than red blood cells. These parameters are mentioned specifically in the present specification at page 7, lines 22-32. Pittman, ¶ 10; Schmitt, ¶ 10.

In contrast, the present invention, by using a scattering subset of wavelengths, in addition to an absorbance subset, with molar extinction coefficients for each constituent component at each wavelength, is able to accommodate all contributors to scattering in a sample of whole blood of unknown composition. Thus, the present invention accomplishes, for the first time, the quantification of the concentrations of the constituent components of whole blood of unknown composition, corrected for the effects of radiation scattering.

For these reasons, Applicants respectfully assert that independent claim 1, and claims 2-36, dependent therefrom, would not have been obvious in light of the teachings of the Anderson *et al.* reference. *See also,* Pittman, ¶¶ 12-14; Schmitt, ¶¶ 12-16.

Further, the Anderson *et al.* reference does not contemplate the correction of the calculated concentrations of constituent components for the effects of finite spectral bandwidth of the wavelengths on the extinction coefficients of each constituent component, as required by dependent claim 10.

In addition, the Anderson *et al.* reference does not disclose or suggest the selection of an absorbance subset of four radiation wavelengths using the minimization of the computed error

index, as required by claims 11 and 29, and does not teach the specific ranges or sets of wavelengths recited in dependent claims 12-19 and 30-33.

Moreover, Anderson *et al.* do not disclose or suggest the correction of the calculated concentrations of the constituent components for the effects of light scattering by red cells, nor do they contemplate the concept of the iterative determination of a red blood cell scattering vector (claims 20-22). Similarly, Anderson *et al.* do not contemplate the correction of the calculated concentrations of the constituent components for the effects of non-specific light scattering, nor do they contemplate the iterative determination of a non-specific scattering vector (claims 23-25). These arguments apply equally to claims 26-28, which require the accommodation of scattering, both by red blood cells and non-specific sources.

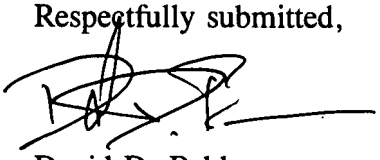
In light of the foregoing points of discussion, Applicants respectfully request the Examiner to withdraw the rejection of claims 1-33 under 35 U.S.C. § 102(b) or under § 103.

CONCLUSION

Applicants believe the foregoing to be a full and complete response to the subject office action, and respectfully request the withdrawal of the rejection of claims 1-33 and the issuance of a timely notice of allowance for claims 1-36. Should the Examiner believe that another

personal discussion would be helpful, she is encouraged to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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